Therapeutic options in recurrent glioblastoma-An update

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Abstract: INTRODUCTION Standards of care are not yet defined in recurrent glioblastoma. METHODS We reviewed the literature on clinical trials for recurrent glioblastoma available in PubMed and American Society of Clinical Oncology (ASCO) abstracts until June 2015. RESULTS Evidence is limited due to the paucity of randomized controlled studies. Second surgery or re-irradiation are options for selected patients. Alkylating chemotherapy such as nitrosoureas or temozolomide and the vascular endothelial growth factor (VEGF) antibody, bevacizumab, exhibit comparable single agent activity. Phase III data exploring the benefit of combining bevacizumab and lomustine are emerging. Novel approaches in the fields of targeted therapy, immunotherapy, and tumor metabolism are coming forward. Several biomarkers are being explored, but, except for O(6)-methylguanine DNA methyltransferase (MGMT) promoter methylation, none has assumed a role in clinical practice. CONCLUSION Proper patient selection, development of predictive biomarkers and randomized controlled studies are required to develop evidence-based concepts for recurrent glioblastoma.

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Therapeutic options in recurrent glioblastoma – an update

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Abstract

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Conclusion

Proper patient selection, development of predictive biomarkers and randomized controlled studies are required to develop evidence-based concepts for recurrent glioblastoma.

Keywords: Glioblastoma, MGMT, temozolomide, nitrosourea, bevacizumab, immunotherapy

Highlights:

1. Standards of care are incompletely defined in recurrent glioblastoma.
2. The evidence for repeat surgery or reirradiation is limited.
3. Alkylating chemotherapy (nitrosourea, temozolomide) is a widely accepted therapeutic option.
4. Bevacizumab has clinical activity, but an effect on overall survival is uncertain.
5. Individualized treatment concepts should consider age, performance status, *MGMT* promoter methylation status, response to and type of previous regimens and quality of life.

Contents

1. Introduction

2. Scope and objectives

3. Results

3.1 Diagnosis of progression and response

3.2 Surgery at recurrence

3.3 Repeat radiotherapy

3.4 Chemotherapy for recurrent glioblastoma

3.4.1 Nitrosourea monotherapy and combination regimens

3.4.2 Temozolomide monotherapy and combination regimens

3.4.3 Other classical non-alkylating chemotherapy

3.4.4 Bevacizumab monotherapy and combination regimens

3.4.5 Targeted therapy

3.4.6 Immunotherapeutic approaches

3.4.7 Alternative approaches

4. Summary and conclusion

5. Conflicts of interest statement

6. Tables

7. Vitae

8. References

1. Introduction

Despite advances in the understanding of its biology, glioblastoma, the most common malignant brain tumor, remains a devastating disease. Median overall survival (OS) in population-based studies in the US was 8.1 months in the period of 2000 – 2003 and 9.7 months from 2005 -2008 [1]. In 2005, the current standard of care in newly diagnosed glioblastoma was established based on the trial of the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) showing prolonged median OS of 14.6 months by addition of temozolomide (TMZ) during and after radiotherapy compared to radiotherapy alone (12.1 months) [2]. Promoter methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene was established as a predictive biomarker for benefit from TMZ in newly diagnosed glioblastoma [3]. For elderly patients, e.g., older than 65-70 years, the standard of care for newly diagnosed glioblastoma without *MGMT* promoter methylation or unknown *MGMT* status is radiotherapy alone [4]. In contrast, elderly patients with glioblastoma with *MGMT* promoter methylation should receive TMZ without or with radiotherapy [5-7].
Tumor recurrence occurs in almost all patients. Currently, no standard of care is established in recurrent or progressive glioblastoma [7]. Despite numerous clinical trials, the identification of effective therapies is complicated by the lack of appropriate control arms, selection bias, small sample sizes and disease heterogeneity [8].

2. Scope and objectives

Here we review clinical efficacy data for the treatment of patients with recurrent (=progressive) glioblastoma with focus on prospective and randomized clinical trials published in PubMed or as ASCO abstract reports until June 2015. Phase I or retrospective studies were only included in case of lack of prospective data, or for historical or innovative importance. We discuss the current status of diagnosis of tumor response and progression. The therapeutic value of repeat surgery and radiotherapy as well of different systemic treatment regimens including nitrosoureas, temozolomide, bevacizumab, targeted therapies, combinational approaches or novel concepts including immunotherapy in patients with recurrent glioblastoma are reviewed, with a focus on new data emerging since 2013 [8]. Finally, the impact of these clinical trials on current clinical practice in recurrent glioblastoma is discussed.

3. Results

3.1 Diagnosis of progression and response

Criteria for response and progression in glioblastoma have remained a matter of debate for the past decades. Still, MRI imaging every 2 to 3 months remains the gold standard for diagnosis of response or progression in glioblastoma. However, several concerns have been raised regarding the Macdonald criteria, being the standard tool for response evaluation until 2010 [9]. Limitations included the observation of "pseudoprogression" as a transient increase of contrast-enhancing tumor especially within the first 3 months after completion of radiotherapy as well as "pseudoresponses" with divergent effects on contrast-enhanced T1-images versus T2/fluid-attenuated inversion recovery (FLAIR) sequences especially with use of antiangiogenic agents. Since 2010, the updated criteria for Response Assessment in Neuro-Oncology (RANO) add restricted parameters for diagnosis of progressive disease within 3 months after completion of radiochemotherapy and integrate the evaluation of T2/FLAIR sequences as well of corticosteroid use [10]. Recently, the same group has provided an international consensus protocol based on the development of the EORTC Brain Tumor Group for uniform evaluation in clinical trials and practice [11]. Comparing overall response rates and progression-free survival (PFS) in different clinical trials using either Macdonald or RANO criteria is thus difficult. To date, the RANO criteria are considered the best standardized tool for evaluation of response and progression in glioblastoma. Several imaging techniques and modalities have been proposed for the identification of response or progression as well as prognostic or predictive tools for therapeutic efficacy, e.g. perfusion imaging, dynamic susceptibility contrast, apparent diffusion coefficient and MR spectroscopy [12-18]. However, these studies are limited in patient size and/or adequate control groups. To date, in case of suspected pseudoprogression, repeated MRI imaging in shortened time intervals is recommended, while usually maintaining treatment. O-(2-(18)F-fluoroethyl)-L-tyrosine)-positron emission tomography ((18)F-FET-PET) may help to identify pseudoprogression versus early progression after radiochemotherapy, too [19].

3.2 Surgery at recurrence

The role of repeat surgery in patients with progressive or recurrent glioblastoma remains controversial. Some retrospective studies proposed a survival benefit after reoperation [20-23] while others did not [24]. Limitations of most of the studies

include high probability of selection bias and lack reasonable controls for comparison [25]. Factors proposed for benefit of surgery and decision-making represent general prognostic factors for glioblastoma, such as age, *MGMT* promotor methylation, performance status, tumor volume, extent of resection, and tumor localization. A scale including tumor involvement in non-eloquent areas, small tumor volume (< 50 cm^3) and good performance status (KPS>80%) was proposed in 2010 and modified to a score comprising KPS and ependymal involvement for decision making regarding reoperation, based on retrospective data [26, 27].

Few prospective data sets on repeat surgery are available. A prospective registry study of 764 patients with glioblastoma analyzed over a 7-year period (2004-2010) with one third of patients reoperated at recurrence did not suggest a benefit of repeat surgery (HR 1.02), however, no detailed patient stratification for prognostic variables was available [28]. Similarly, in a meta-analysis of 8 prospective phase I and II trials comprising 300 patients with recurrent glioblastoma repeat surgery was not an independent predictor for PFS and OS [29]. A post-hoc analysis of the prospective DIRECTOR trial evaluating two different dosing schemes of TMZ in patients with recurrent glioblastoma did not show a difference in overall survival in patients with (n=71) versus without (n=34) surgery at recurrence. However, when stratifying for extent of resection (n=59 available for analysis), there was superior survival in patients with complete resection of gadolinium-enhancing tumor (n=39) [30]. Similarly, a prospective non-randomized registry for patients with repeat surgery identified a correlation between (high) extent of resection and survival [31].

Beyond an expected therapeutic efficacy of repeat surgery, the acquisition of tumor tissue at recurrence might be valuable in some situations, e.g. for diagnosis of recurrent disease (e.g. versus radiation necrosis), confirmation of initial histology and/or determination of molecular markers for biomarker-based decision making.

3.3 Repeat radiotherapy

Re-irradiation is a similarly controversial option for patients with recurrent glioblastoma. Evidence-based clinical decision making is impeded by the lack of prospective and randomized trial design and high probability of selection bias in single arm studies. Main concerns include safety with regard to radiation necrosis and neurocognitive impairment as well as limited efficacy at recurrence after initial irradiation. Without establishment in prospective or controlled studies, for fractionated

stereotactic radiotherapy total doses between 30-36 Gy in 2-3.5 Gy fractions with or without intensity modulation have been used [32, 33]. Radiosurgery is less frequently used in glioblastoma. As favorable variables for selecting patients likely to benefit from re-irradiation again general prognostic factors such as young age, high KPS or small tumor size have been proposed [32, 34-37]. Different reports exist regarding the preferred time interval to initial radiation for benefit from re-irradiation, favoring either an interval of less than 6 months [35] or more than 6 or even 12 months [37, 38].

Several combination partners have been proposed for re-irradiation with the hypothesis of synergistic effects. A randomized phase II study evaluating re-irradiation with and without the addition of a CD95 ligand-binding fusion protein, APG101, showed poor outcome in the re-irradiation-only arm (PFS-6 3.8%, median PFS 2.5 months) but significantly higher PFS-6 (20.7%) and median PFS (4.5 months) in the combination arm. However, median OS was equal in both groups with 11.5 months. Presence of CD95L as determined by promoter methylation may identify patients benefitting from APG101 [39]. Several studies evaluated the combination of bevacizumab with re-irradiation with the hypothesis that vascular normalization results in improved oxygenation of tumor tissue and thereby increases the effect of radiation. With heterogeneous cohorts of WHO grade III (n=6, n=14, n=12) and glioblastomas (n=8, n=43, n=42) treated with re-irradiation with and without bevacizumab a higher median PFS (5.7 vs. 3.7, 5.6 vs. 2.5, and 6 vs. 4 months) and higher median OS (8.3 vs. 14.3, 8.6 vs. 5.7, 11 vs 8.3 months) were reached in 2 of 3 retrospective studies in the bevacizumab cohort [40-42]. In the study of Minniti and colleagues the non-bevacizumab group received fotemustine. A prospective study evaluating stereotactic radiosurgery plus bevacizumab (n=8 patients with anaplastic glioma, n=7 with glioblastoma) reported a median PFS of3.9 and median OS 14.4 months. Toxicity included one grade 3 and two grade 2 CNS toxicities [43].

3.4 Chemotherapy for recurrent glioblastoma

The landscape of chemotherapeutic trials in recurrent glioblastoma is influenced by the historical evolution of the standard of care for newly diagnosed and recurrent disease, heterogeneity of inclusion criteria, choice of endpoints and response criteria, pretreatment and patient characteristics. In addition, most studies are non-

comparative or fail to use a control arm lacking the experimental drug.
Some, especially older trials include both anaplastic gliomas and glioblastoma. Trials conducted before the establishment of standard TMZ-based radiochemotherapy in 2005 commonly included TMZ-naïve patients. Different endpoints and use of different response criteria further impede comparability of trials. Six-months PFS rate (PFS-6) and median OS from the time of treatment for recurrence are reasonable endpoints for clinical trials in recurrent glioblastoma [44], however, criteria of response and progression are still moving targets.

3.4.1 Nitrosourea monotherapy and combination regimens

Nitrosoureas (e.g., carmustine [BCNU], lomustine [CCNU], nimustine [ACNU], fotemustine) are DNA alkylating agents that cross the blood-brain barrier and have been extensively used in glioma treatment. They may induce considerable hematological toxicity with long-lasting bone marrow suppression, liver and renal toxicity, and, specifically carmustine, interstitial lung disease. After approval of TMZ in 1999 for recurrent glioblastoma based on efficacy data of 2 phase II trials and a favorable safety profile [45, 46], nitrosoureas were used less frequently. Their use rose again when TMZ became standard of care in newly diagnosed glioblastoma.
Table 1 summarizes nitrosourea-based trials in recurrent glioblastoma. There are 5 single arm phase II trials with nitrosourea monotherapy (1 with carmustine, 4 with fotemustine at different dosing regimens) [47-51] and 6 randomized phase II or phase III trials comprising one therapeutic arm with nitrosourea monotherapy: 5 trials with lomustine [52-56] and 1 trial with carmustine where data for patients treated with carmustine (n=29) were not separately reported but summarized in a common “control” arm with 27 patients receiving TMZ [57]. All but 3 trials were conducted at the first recurrence after TMZ-based standard radiochemotherapy. One study was done in chemotherapy-naïve-patients [47], one study did not disclose previous chemotherapy except exclusion of nitrosourea, bevacizumab or investigational agents [53], one study reported previous chemotherapy in about 60% of the patients without details [57]. PFS-6 ranged between 17.5% and 61.5% and median OS between 6.0 and 11.1 months for monotherapy of nitrosourea agents.
Notably, in the randomized studies, lomustine as monotherapy showed comparable results with the investigational agents enzastaurin, cediranib, galunisertib or bevacizumab [52-55], pointing towards relevant single agent activity of the “control”

agent or lack of efficacy of the experimental agents The combination of lomustine plus bevacizumab showed prolonged median PFS and OS and higher PFS-6 than the single agents in the BELOB phase II trial [54]. However, the combination treatment at least with the higher dose of lomustine with 110 mg/m^2 exhibited more hematological toxicity leading to the dose reduction to 90 mg/m^2 when combined with bevacizumab. Another randomized phase II trial evaluated the combination of lomustine with 90 mg/m^2 with bevacizumab 5 mg/kg every 3 weeks versus bevacizumab alone at 10 mg/kg every 2 weeks in a heterogenous cohort of patients with glioblastoma at 1st, 2nd or 3rd relapse. The authors emphasized a benefit for the subgroup of patients at 1st relapse in the combination arm with a median OS with 13.1 months versus 8.8 months in the monotherapy arm without disclosing the number of patients in this subgroup and without reporting PFS and OS results of the intent-to-treat population [58]. Another phase II study evaluated the combination of nitrosourea, namely fotemustine with bevacizumab, however, not in a randomized but single-arm design [59]. PFS-6-rate of 42.6% was similar with the BELOB trial with a median OS of 9.1 months (BELOB: 11 months [54]). Again, hematological toxicity was relevant with 22% of the patients discontinuing fotemustine due to grade 3 or 4 myelotoxicity. The promising efficacy signal of the combination of nitrosoureas with bevacizumab of phase II trials was not confirmed in the EORTC 26101 phase III trial comparing lomustine plus bevacizumab with lomustine alone in patients with recurrent glioblastoma which did not report a difference in OS (8.6 versus 9.1 months), although prolonged PFS (1.5 versus 4.2 months) was confirmed [56].
Other studies regarding nitrosourea combination therapies for recurrent disease are mostly retrospective. One phase II trial evaluating the combination of carmustine and irinotecan showed PFS-6 of 30.3%, median PFS of 3.9 and median OS of 11.7 months. Beyond hematologic toxicities, mainly grade 1 and 2, frequent diarrhea (69% grade 1 and 2, 7.1% grade 3) and 9.5% cholinergic syndrome were seen [60]. The combination of TMZ with nitrosoureas, fotemustine or carmustine, was evaluated in 2 prospective studies, both with severe and frequent hematologic toxicities leading to dose reductions and early stop of enrolment in one study without clear efficacy signals beyond single agent activity [61, 62].
In summary, the different nitrosoureas show probably comparable efficacy as single agents and remain to be one standard of care at least for current clinical trials. It is likely to expect that clinical efficacy will be more prominent in patients with tumors

with *MGMT* promoter methylation [54, 63]. The substantial toxicity profile limits combination with other agents.

3.4.2 Temozolomide monotherapy and combination regimens

Table 2 provides an overview on clinical trials of TMZ monotherapy, randomized trials with a TMZ monotherapy arm and combination regimens. TMZ was approved in 1999 for recurrent glioblastoma based on the data of 2 phase II trials.

TMZ was superior to procarbazine in patients, 60% of which were pretreated with nitrosoureas, with a PFS-6 rate of 21% vs. 8% and median OS prolonged by 1.5 months [46]. A single-arm phase II trial in 126 patients led to a PFS-6 rate of 18% [45]. Both trials used a schedule of TMZ 150-200 mg/m^2 for 5 out of 28 days. Other prospective studies mainly without previous TMZ treatment using this schedule showed similar PFS-6 rates ranging from 21 to 24% [64-67].

Alternative schedules of TMZ were developed aiming at overcoming TMZ resistance or exerting additional biologic effects, e.g. on angiogenesis. The main alternative schedules (Table 2) comprise low dose daily TMZ (40-50 mg/m^2/d), 1-week-on/1-week-off (150 mg/m^2 for 7 days every 14 days), and 3-week-on/1-week-off (75-100 mg/m^2 for 21 days every 28 days). Grade 3 and grade 4 hematologic toxicities were observed in most of the studies without apparent differences between the schedules. Since most of the studies were conducted as single-arm monotherapy trials with different inclusion criteria e.g. regarding number of recurrences and pretreatment characteristics, comparison of efficacy outcome is limited. Yet, it seems very unlikely that there are relevant differences between the various dose-intensified TMZ regimens, and their superiority over standard dose TMZ for patients experiencing recurrence after a TMZ-free interval has not been demonstrated either. The RESCUE phase II trial evaluated the timing of TMZ rechallenge with prospective grouping of patients. Patients who received continuous TMZ for progression during the first 6 cycles of adjuvant TMZ and those patients with a treatment-free interval longer than 2 months showed comparable PFS-6 rates of 27.3 and 35.7% (median PFS 3.6 and 3.7 months) deriving more benefit than those patients receiving TMZ beyond the standard 6 adjuvant cycles but without a treatment-free interval (PFS-6 7.4%, median PFS 1.8 months) [68].

Beyond the randomized trial leading to the approval of TMZ mentioned above, two other randomized trials with TMZ monotherapy as one of the treatment arms have

been published, a direct comparison with the combination of procarbazine, lomustine and vincristine (PCV) before TMZ became first-line standard [69] and a negative trial for the epidermal growth factor recetor (EGFR) tyrosine kinase inhibitor afatinib [70] (Table 2 and 4), indirectly supporting the role of TMZ at recurrence.

The DIRECTOR trial compared TMZ 120 mg/m^2 for 7 days every 14 days with 3-week-on/1-week-off 80 mg/m^2 for 21 days every 28 days and found no difference in outcome between these two regimens [71]. However, this trial established the role of *MGMT* promotor methylation as a prognostic marker for benefit of TMZ in recurrent glioblastoma patients, with a PFS-6 of 39.7% in patients with *MGMT* promoter-methylated tumors versus 6.9% without *MGMT* promoter methylation, in a prospective manner. The benefit of TMZ at recurrence thus seems limited to patients with tumors with *MGMT* promoter methylation.

Numerous studies evaluated TMZ-based combination regimens in recurrent glioblastoma. Beyond the combination with nitrosoureas already discussed, the following combination partners have been prospectively evaluated in single-arm designs:

The anti-vascular endothelial growth factor (VEGF) antibody bevacizumab [72-75], interferon-α2b [76], the multikinase inhibitor sorafenib [77], O6-benzylguanine [78], irinotecan [79], cisplatin [80, 81], liposomal doxorubicine [82] and ABT-414, an EGFR-targeted antibody-drug conjugate conjugated to monomethylauristatin F [83]. So far, these trials have failed to provide convincing efficacy signals beyond single agent activity of TMZ.

3.4.3 Other classical non-alkylating chemotherapy

Beyond chemotherapy with alkylating agents (TMZ or nitrosoureas), other classical non-alkylating chemotherapeutics have been explored in the treatment of recurrent glioblastoma. A detailed listing of all trials with these agents, mostly conducted as single arm studies, would be beyond the scope of this review. Carboplatin (CABARET trial) and irinotecan (BRAIN trial) have been evaluated in randomized phase II trials as add-ons to bevacizumab (Table 3) [84, 85]. Both trials were negative showing no difference in outcome but additional toxicity in the treatment arms with carboplatin and irinotecan.

3.4.4 Bevacizumab monotherapy and combination regimens

Table 3 summarizes trials with single-arm monotherapy, randomized trials and single arm combination containing bevacizumab. Bevacizumab was approved in 2009 for the treatment of recurrent glioblastoma by the FDA and in several other countries based on the results of 2 uncontrolled phase II trials with overall response rates of about one third of the patients and with PFS-6 rates of 42.6 and 29% [85, 86]. In Europe, approval was refused because of the lack of a bevacizumab-free control arm. There are 9 phase II trials with a bevacizumab monotherapy arm, 3 of them single-arm studies [86-88], 5 trials compared bevacizumab with bevacizumab plus another agent, such as irinotecan [85], carboplatin [84], the histone-deacetylase inhibitor vorinostat [89], the multikinase inhibitor dasatinib [90] or lomustine [58]. Only one trial had a bevacizumab-free control arm with lomustine [54]. Most of these trials used bevacizumab at 10 mg/kg IV every 2 weeks except one study with 15 mg/kg IV every 3 weeks [87] and one study with 5 mg/kg IV every 3 weeks when combined with lomustine [58]. Toxicity of bevacizumab was mainly non-hematologic including hypertension, thrombembolic events, fatigue, and impaired wound healing. Overall response rates were similar in most trials with around one third of the patients mainly assessed by Macdonald criteria but also by RANO [54, 90], while one trial only reports 6%, assessed by RANO criteria [84]. PFS-6 rates ranged from 18% to 42.6% and median OS from 6.5 to 9.2 months. In the randomized trials adding another experimental agent to bevacizumab (irinotecan, carboplatin, vorinostat or dasatinib) versus bevacizumab alone, both arms showed comparable efficacy leading to the conclusion of poor efficacy of the experimental agent without valid evidence regarding the single agent activity of bevacizumab [84, 85, 89, 90]. The BELOB trial comprising a bevacizumab-free control arm showed comparable single agent activity of bevacizumab versus lomustine. However, as already discussed, median OS of the combination of bevacizumab and lomustine was superior to single agent activity in this phase II trial in contrast to the EORTC 26101 phase III trial showing no difference in OS of the combination versus lomustine alone [54, 56].

More than one dozen prospective trials evaluated bevacizumab in combination with other experimental agents in a single-arm design (Table 3). The trials combining bevacizumab with nitrosoureas or TMZ have already been mentioned in Table 1-2. Surprisingly, the combination of bevacizumab with TMZ [72-75] seems less promising than the combination with nitrosoureas [54, 58, 59]. However, no direct comparisons are available and the trials evaluating bevacizumab plus temozolomide were

conducted in part in highly pretreated patient populations [72-74]. Five phase II trials evaluated the combination of irinotecan with bevacizumab [91-95], two trials added a third combination partner, cetuximab [96] or carboplatin [97]. PFS-6 rates ranged between 28 and 50.3% and median OS between 6.7 and 9.7 months. Other experimental agents that were combined with bevacizumab are etoposide [98], the mTOR inhibitor temsirolimus [99], the EGFR-targeted tyrosine kinase inhibitor erlotinib [100], the multikinase inhibitor sorafenib [101], the histone deacetylase inhibitors panobinostat [102] or vorinostat [103].

No efficacy signal beyond the data for bevacizumab monotherapy was seen except for lomustine at phase II with negative results in the comparative phase III trial (EORTC 26101) [54, 56]; in addition, some of the combination trials reported increased toxicity.

In the clinic, after progression on a bevacizumab-containing regimen, bevacizumab is often continued fearing a rebound effect when stopping antiangiogenic therapy and data from metastatic colorectal cancer support this concept [104]. This clinical practice so far was lacking evidence from prospective and controlled clinical trials. This question was prospectively addressed with the cohort of the CABARET randomized phase II trial comparing bevacizumab monotherapy with bevacizumab plus carboplatin [105]. Upon progression of one of the two regimens, patients were randomized again to continue or cease bevacizumab. Patients previously receiving bevacizumab monotherapy could receive carboplatin or supportive care and those treated with combined bevacizumab plus carboplatin ceased carboplatin and could receive TMZ, etoposide or supportive care according to clinician choice. Forty-eight of initially 120 patients (40%) were available for randomization. There were no differences in outcome with a poor overall response of 0% in both arms, median PFS of the group continuing bevacizumab versus ceasing was 1.8 versus 2.0 months, OS was 3.4 versus 3.0 months.

In conclusion, there is little evidence to continue bevacizumab in patients with glioblastoma after progression on a bevacizumab-containing regimen.

3.4.5 Targeted therapy

In the last decade, a plethora of agents have been suggested for targeting essential pathways in glioblastoma. The pharmacologic agents had commonly been tested *in vitro* or *in vivo* or both before. Table 4 gives an overview on several phase II studies

conducted with agents targeting receptors or soluble factors involved in angiogenesis, oncogenic pathways or factors presumably involved in tumor cell stemness or tumor invasiveness. Most studies were designed as single-arm trials, some agents were tested in a randomized fashion against lomustine or TMZ. The results of single-arm phase II studies again are likely to be influenced by selection bias, patient heterogeneity and small patient numbers. Those agents tested against lomustine or TMZ failed to prove superiority.

Candidate anti-angiogenic agents other than bevacizumab, e.g. aflibercept, sunitinib, vandetanib or nintedanib failed to give an efficacy signal. Cediranib, a pan-tyrosine kinase inhibitor of VEGFR achieved similar response rates and PFS-6-data as did bevacizumab in phase II [85, 86, 106]. The subsequent phase III trial of cediranib showed comparable but not better efficacy than lomustine. Still, it is surprising that cediranib which is supposed to be similarily active as bevacizumab did not show superiority in combination with lomustine [52]. Further, the clinical development of a placental derived growth factor antibody was stopped early for presumed lack of activity [107].

Targeted agents aiming to inhibit oncogenic pathways such as enzastaurin, everolimus, PX-866, selinexor or dasatinib showed disappointing results [53, 108-111]. The phase II trial evaluating the multikinase inhibitor dasatinib only included patients with activation or overexpression of ≥2 putative dasatinib targets (ie, SRC, c-KIT, EPHA2, and PDGFR), nevertheless with poor efficacy results [111]. A placebo-controlled randomized phase II trial evaluating galunisertib, an inhibitor of transforming growth factor (TGF)-β receptor-1, shown to be involved in multiple pathogenic processes in glioblastoma *in vitro*, did not improve outcome when combined with lomustine [55]. However, the trial design containing a placebo-controlled active control (lomustine+placebo) at least allows reasonable conclusions on activity. The integrin inhibitor cilengitide tested in two dosing regimens in a randomized fashion, without a control arm lacking the experimental agent, showed a trend to prolonged survival at the higher dose [112]. A novel principle, the inhibition of histone deacetylase aiming to target epigenetic gene regulation, with agents such as vorinostat or panobinostat so far failed to provide efficacy signals [89, 102, 113, 114]. However, based on the mechanism, the combination with cytoxic drugs such as lomustine or temozolomide might rather lead to synergistic effects than with bevacizumab. Several EGFR-targeting agents have been developed, such as

gefitinib, erlotinib or afatinib, a strategy effective in EGFR-mutated non-small-cell lung cancer, however, so far with disappointing results in glioblastoma [57, 70, 108, 115]. The phase II trial evaluating afatinib, an irreversible ErbB family blocker, showed that in the biomarker cohort (70 patients, 59%) the median PFS in those patients treated with afatinib monotherapy with EFGRvIII-positive tumors vs -negative tumors was 3.4 vs 1.0 months pointing towards efficacy in subgroups (over-)expressing the target [70]. The efficacy of ABT-414 might be further improved in a target-selected cohort since all patients of an unselected phase I cohort with confirmed response had EGFR amplification [83]. A current phase II trial (Clinicaltrials.gov NCT02343406) investigates whether ABT 414 alone or combined with temozolomide is superior to lomustine or temozolomide re-challenge in recurrent EGFR-amplified glioblastoma. In conclusion, so far none of the targeted agents has proven efficacy beyond the activity of alkylator therapy.

In conclusion, so far none of the targeted agents has proven efficacy beyond the activity of alkylator therapy.

3.4.6 Immunotherapeutic approaches

Therapeutic principles of immunotherapy include immunomodulatory drugs aiming at activating the immune system against the tumor, treatment with oncolytic viruses and different vaccination approaches, either cell-based or antigen-based or both. All approaches theoretically should work best if applied early in the course of the disease to patients with minimal residual disease. This is why the majority of immunotherapeutic studies in glioblastoma today are conducted in the first-line setting and no longer in recurrent glioblastoma.

A promising immunotherapeutic approach is “immune checkpoint inhibition” interfering with inhibitory T cell signaling via programmed death 1 (PD-1), the PD-1-ligand, or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Preliminary data of a phase II study, randomizing patients with recurrent glioblastoma to either nivolumab, a PD-1 antibody, alone or combined with ipilimumab, a CTLA-4 antibody, showed an overall survival rate of 75% at 6 months for both arms pooled [116]. Relevant toxicity including included colitis, cholecystitis, diabetic ketoacidosis, and confusion leading to discontinuation occurred in the combination arm in 50% of the patients. Other checkpoint inhibitors targeting PD-1 (Pembrolizumab, Clinicaltrials.gov NCT02337491) or PD-L1 (MEDI4736, Clinicaltrials.gov

NCT02336165) are currently evaluated in phase II.
A phase I trial in recurrent glioblastoma evaluated TMZ combined with a vaccine of monocyte-derived dendritic cells pulsed with autologous tumor cells previously been exposed to TMZ. Two of 9 patients had objective radiological responses and were progression-free at 6 months [117].
Gliovac, a vaccine composed of autologous and allogene antigens combined with GM-CSF and previous treatment with cyclophosphamide was shown to be safe in phase I and all patients (n=9) were alive at 6 months [118]. A phase II trial (n=41 patients) evaluated a vaccine composed of heat shock peptide protein complexes (HSPPC-96) after repeat tumor resection. PFS-6 of evaluable patients was 29.3%, median PFS 4.4 and median OS 9.8 months [119]. Strict patient selection after inclusion for being “evaluable” (30% were excluded) limits the interpretation of these results. A phase II trial showed promising results for rindopepimut, a vaccine consisting of a peptide sequence of EGFRvIII, plus bevacizumab versus bevacizumab plus control vaccine in bevacizumab-naïve patients (1st or 2nd relapse, n=72). The rindopepimut arm had higher overall response rate (24% vs. 17%), prolonged PFS-6 (27% vs. 11%) and median OS (12 vs. 8.8 months). An association of an anti-EGFRvIII immune titer generation with OS within the rindopepimut arm further supports this approach [120].

3.4.7 Other approaches

Beyond repeat surgery, irradiation, various chemotherapic and immunotherapeutic approaches, two further treatment concepts for recurrent glioblastoma shall be briefly mentioned. One approach comprises a portable device, called tumor-treating alternating electric fields (TTFields/NovoTTF), delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays aiming at physically interfere with cell division. NovoTTF(n=120 patients, 20-24h/d) was evaluated in a randomized phase III trial versus best physicians choice of chemotherapy (n=117 patients: bevacizumab in 31%, irinotecan in 31%, nitrosourea in 25%, carboplatin in 13%, temozolomide in 11% of patients). Median OS was comparable in both groups with 6.1 versus 6.6 months, PFS-6 was 21.4% and 15.1%. Toxicity was limited to moderate and mild skin reactions [121]. The interpretation of these data remains controversial, but the trial was overall as negative as many other trials discussed above.

Another “chemotherapy-free” approach represents the ERGO trial that examined a ketogenic diet in 20 patients with recurrent glioblastoma. With a median PFS of 1.2 and an OS of 7.4 months, there was no evidence of activity [122].

4. Summary and conclusion

Despite a plethora of clinical trials in recurrent glioblastoma, there are no established standards of care beyond alkylating chemotherapy or bevacizumab. The future role of bevacizumab is uncertain since the EORTC 26101 trial failed to demonstrate superiority for OS of lomustine plus bevacizumab over lomustine alone [56]. Many single-arm trials are difficult to interpret because of the lack of a controlled and randomized design and heterogeneous cohorts. Stratification of patients according to prognostic markers and implementation of control groups already in phase II trials may improve design and facilitate data interpretation in future trials. Based on the available clinical data for therapeutic strategies in glioblastoma, some conclusions, illustrated in Figure 1, can be drawn:

- The RANO criteria represent the currently most accepted approach for diagnosis of progression and response in recurrent glioblastoma and the international consensus MRI protocol provides a good working tool for practice and trials.
- The evidence for repeat surgery or reirradiation is limited, calling for prospective randomized trials determining their efficacy.
- Nitrosoureas still represent the most widely accepted standard option for systemic chemotherapy at recurrence
- *MGMT* promotor methylation may emerge as a predictive biomarker for benefit of TMZ rechallenge in recurrent glioblastoma, indirectly disencouraging treatment with TMZ for *MGMT* promoter-unmethylated tumors. The best schedule of TMZ at recurrence has not been defined, and may be scheduling matters less than previously thought.
- There is clinical activity of bevacizumab monotherapy at recurrence, but an effect on overall survival is uncertain. Prospective data from phase II trials pointed towards efficacy of a combination regimen with nitrosoureas which was not confirmed in phase III.
- Immunotherapeutic concepts are currently under evaluation for newly diagnosed and recurrent glioblastoma, with promising preliminary data for rindopepimut, warranting further efforts exploring further immunotherapeutic agents even in the

recurrent setting, e.g., immune checkpoint inhibitors

In summary, treatment concepts for patients with recurrent glioblastoma in clinical practice should be somewhat individualized and take into account age, performance status, *MGMT* promoter methylation status and response to previous regimens as well as quality of life with regard to expected toxicities. To improve evidence on treatment options, patients should be treated within carefully designed clinical trials. Rebiopsies may be required more often to ascertain molecular tumor status as more targeted therapies become available. Further preclinical and clinical investigation is needed to improve the prognosis for patients with recurrent glioblastoma.

5. Conflicts of interest statement:

KS has received honoraria from Roche for advisory board participation.

WW has received research grants from Apogenix, Boehringer Ingelheim, Eli Lilly, immatics, MSD and Roche as well as honoraria for lectures or advisory board participation from MSD and Roche. WW is or has been the coordinating investigator for sponsored clinical trials evaluating APG101 (Apogenix), bevacizumab (Roche), galunisertib (Eli Lilly), temozolomide (MSD) and temsirolimus (Pfizer).

MW has received research grants from Acceleron, Actelion, Alpinia Institute, Bayer, Isarna, MSD, Merck & Co, Novocure, PIQUR and Roche and honoraria for lectures or advisory board participation or consulting from Celldex, Immunocellular Therapeutics, Isarna, Magforce, MSD, Merck & Co, Northwest Biotherapeutics, Novocure, Pfizer, Roche and Teva.

6. Tables

Table 1. Nitrosourea monotherapy and combination regimens[1]

Design	No. of relapse, no. of patients	Pre-treatment	Treatment	ORR (%)	PFS-6 (%)	mPFS (months)	mOS (months)	Ref.
Single-arm monotherapy trials								
Phase II	n=40	RT	BCNU 80 mg/m^2 on days 1-3 q8wk for max 6 cycles	15%	17.5%	NA	7.5	[47]
Phase II	1st, n=27	RT/TMZ+TMZ	FOT IV 100 mg/m^2 qwk for 3 wks (induction), then q3wk (maintenance)	30%	48.2%	5.7	9.1	[48]
Phase II	1st, n=43	RT/TMZ+TMZ	FOT 75-100 mg/m^2 qwk for 3 wks, after 5-wk break 100 mg/m^2 q3wk for ≤1 yr	7%	20.9%	1.7	6.0	[49]
Phase II	1st, n=50	RT/TMZ+TMZ	FOT 100 mg/m^2 qwk for 3 wks (induction), 4- to 6-wk break, then FOT 100 mg/m^2 q3wk (maintenance)	18%	52%	6.1	8.1	[51]
Phase II	1st, n=40	RT/TMZ+TMZ	FOT IV 80 mg/m^2 on days 1, 15, 30, 45, and 60 (induction), then 80 mg/m^2 q4wk (maintenance)	25%	61%	6.1	11.1	[50]
Randomized trials								
Phase II, randomized	1st, CTR: n=29 (BCNU), n=27 (TMZ), n=52 evaluable; n=54 (ERL)	RT+/-Chemo (64% CTR/ 65% ERL)	CTR (BCNU 60 mg/m^2 on days 1-3 q8wk (max 5 cycles) *or* TMZ 150-200 mg/m^2 (5/28) *or* ERL 150-200 mg/d	10% (CTR), 4% (ERL)	24% (CTR), 11% (ERL)	2.4 (CTR), 1.8 (ERL)	7.3 (CTR), 7.7 (ERL)	[57]
Phase III, randomized 2:1	1st: n=70 (CCNU), n=129 (Enzastaurin) 2nd: n=21 (CCNU), n=45 (Enzastaurin)	RT+/-Chemo (NA, no nitrosourea)	CCNU 100-130 mg/m^2 q6wk *or* Enza 500 mg/d (1125 mg on day 1)	4% (CCNU), 3% (Enza)	19% (CCNU), 11% (Enza)	1.6 (CCNU), 1.5 (Enza)	7.1 (CCNU), 6.6 (Enza)	[53]
Phase III, double-blind, randomized 1:2:2	1st,n=65 (CCNU) n=131 (CED), n=129 (CED+CCNU)	RT/TMZ+TMZ	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	8% (CCNU), 14 %(CED), 16%, (CED+ CCNU)	24.5% (CCNU), 16% (CED), 34.5 % (CED+CCNU)	2.7 (CCNU), 3.1 (CED), 4.2 (CED+CCNU)	9.8 (CCNU), 8.0 (CED), 9.4 (CED+CCNU)	[52]
Phase II, randomized	1st, n=50 (BEV), n=46 (CCNU), n=44 (BEV+CCNU)	RT/TMZ+TMZ	BEV 10 mg/kg q2wk *or* CCNU 110 mg/m^2 q6wk *or* BEV q2wk +CCNU 90 (-110) mg/m^2 q6wk	38% (BEV), 5% (CCNU), 34% (BEV+CCNU)	18% (BEV), 11% (CCNU), 41% (BEV+CCNU)	3 (BEV), 2 (CCNU), 11 (BEV+CCNU)	8 (BEV), 8 (CCNU), 11 (BEV+CCNU)	[54]
Phase II, randomized 2:1:1, placebo-controlled	NA, n=79 (CCNU+G), n=39 (G), n=40 (CCNU+P)	NA	CCNU q6w +Galunisertib (CCNU+G) *or* Galunisertib (300mg/d) for 14 days q28d alone (G)	1% (CCNU+G), 5% (G), 0% (CCNU+P)	NA	1.8 (CCNU+G), 1.8 (G), 1.9 (CCNU+P)	6.7 (CCNU+G), 8 (G), 7.5 (CCNU+P)	[55]

			or CCNU q6wk +placebo (P+CCNU)					
Phase II, randomized	1st,2nd, 3rd, n=68 evaluable pts	RT/TMZ+TMZ+/- other	BEV 10 mg/kg q2wk *or* BEV 5 mg/kg q3wk+ CCNU 90 mg/m^2 q6wk	NA	NA	4.1 (BEV), 4.3 (BEV+CCNU)	NA (ITT); Pts with 1st relapse: 8.8 (BEV), 13.1 (BEV+CCNU)	[58]
Phase III, randomized 2:1	1st, n=288 (CCNU+BEV), n=149 (CCNU)	RT/TMZ+TMZ	CCNU 90 mg/m^2 q6wk + BEV 10 mg/kg q2wk *or* CCNU 110 mg/m^2 q6wk	NA	NA	4.2 (CCNU+BEV), 1.5 (CCNU)	9.1 (CCNU+BEV), 8.6 (CCNU)	[56]
Single-arm combination therapy trials								
Phase II	2nd, n=42	RT+ TMZ	BCNU (100 mg/m^2) on days 1+CPT-11 (175 mg/m^2) on days 1-3 q1wk for 4 wks, cycles of 6 wks	21.4%	30.3%	3.9	11.7	[60]
Phase II	NA, n=38	RT+/-chemo (10.5%)	BCNU (150 mg/m^2) +TMZ 550 mg/m^2 q6wks	5.6%	21%	2.5	7.8	[61]
Prospective	NA, n=20 (n=10 evaluable for outcome)	RT/TMZ+TMZ	TMZ 150 mg/m^2 for 7 days q14d +FOT 110 mg/m^2 monthly q14d	NA	40%	4.3	NA	[62]
Phase II	1st,n =54	RT/TMZ+TMZ	BEV 10 mg/kg q2wk +FOT 75 mg/m^2 on day 1 and day 8, then q3wk	52%	42.6%	5.2	9.1	[59]

Abbreviations: BCNU, carmustine; CCNU, lomustine; CED, cediranib; CPT-11, irinotecan; CTR, control arm; d, day; Enza, enzastaurin; ERL, erlotinib; FOT, fotemustine; G: Galunisertib; ITT, intention-to-treat population; max, maximum; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; P, placebo; PFS, progression-free survival; pts, patients; q, every; Ref, reference; RT, radiotherapy; TMZ, temozolomide; wk, week;

[1] All data presented for glioblastoma patients only. In case, the study was designed for different patient populations, only the respective data for glioblastoma patients were included in the table.

Table 2. Temozolomide monotherapy and combination regimens[1/2]

Design	No. of relapse, no. of patients	Pre-treatment	Treatment	ORR (%)	PFS-6	mPFS (months)	mOS (months)	Ref.
Single-arm monotherapy trials								
Phase II	1st, n=126	RT +/- nitrosourea (40%)	Chemo-naïve pts: TMZ 200 mg/m^2/d for 5 days q28d Pts with previous chemotherapy: TMZ 150 mg/m^2/d for 5 days q28d	8%	18%	2.1	5.4	[45]
Phase II	2nd, n=22	RT+PCV	TMZ 150 mg/m^2/d for 5 days q28d	23%	32%	NA	7.6	[65]
Phase II	2nd, n=42	RT+PCV	TMZ 150 mg/m^2/d for 5 days q28d	19%	24%	NA	7.0	[66]
Phase II	NA, n=28	RT (all but 1) +/- chemo (mostly nitrosourea)	TMZ 75 mg/m^2/d for 42 days q70d	0%	19%	2.3	7.7	[123]
Phase II	1st, n=12; 2nd and 3rd, n=9	RT (all) +/- nitrosourea (43%)	TMZ 150 mg/m^2 for 7 days q14d	10%	48%	4.9	NA	[124]
Prospective	1st, n=13	RT	TMZ 200 mg/m^2/d for 5 days q28d, max 4 cycles	NA	21%	NA	NA	[67]
Phase II	1st, n=33	RT	TMZ 75 mg/m^2/d for 21 days q28d	9%	30%	3.7	9.2	[125]
Prospective	NA, n=12	RT+TMZ+/-ACNU (n=1), PCV (n=2)	TMZ 40 mg/m^2/d	17%	NA	6	11	[126]
Prospective	NA, n=19	RT (all) +/- chemo (mostly nitrosourea)	TMZ 150-200 mg/m^2/d for 5 days q28d	24%	22%	2.2	9.9	[64]
Phase II	NA, n=64	RT+/-chemo (n=41 nitrosourea, n=9 TMZ+nitrosourea)	TMZ 150 mg/m^2 for 7 days q14d	NA	43.8%	5.5	NA	[127]
Phase II	1st, n=48; ≥2: n=20	RT+/- chemo (previous non-nitrosourea: chemo n=7; nitrosourea: n=33)	TMZ 200 mg/m^2 initial dose, then 9 consecutive doses at 90-100 mg/m^2 q12h for 28 days;	31%	35%	4.2	8.8	[128]
Phase II	NA, n=27 GB, n=20 AG	RT+chemo (93% TMZ 1st line, 49% at 2nd recurrence), some nitrosourea	TMZ 85 mg/m^2 for 21 days q28d	7%	0	NA	5.1[1]	[129]
Phase II	1st, n=33 (early), n=27 (extended) n=28 (rechallenge) per timing of progression during/after adjuvant therapy	RT+TMZ/TMZ	50 mg/m^2/d continuous (max. 1 year)	NA	23.9% (all groups), 27.3% (early), 7.4% (extended), 35.7% (rechallenge)	NA (all groups) 3.6 (early), 1.8 (extended) 3.7 (rechallenge)	9.3 (all groups)	[68]
Phase II	1st, n=38	RT+TMZ/TMZ	40-50 mg/m^2/d	5%	32.5%	3.9	9.4	[130]

Phase II	1st, n=27	RT+TMZ/TMZ	TMZ 130 mg/m^2 for 7 days q14d, max. 1 year	11.1%	33.3%	4.2	6.9	[131]
Phase II	1st, n=58	RT+TMZ/TMZ	75-100 mg/m^2/d for 21 days q28d	13%	11%	1.8	11.7	[132]
Phase II	1st, n=12, 2nd, n=18, ≥3, n=10	RT+TMZ/TMZ+ other	TMZ 150 mg/m^2 for 7 days q14d	NA	10%	1.8	5	[133]
Randomized trials								
Phase II, randomized	1st, n=112 (TMZ), n=113 (PCB)	RT +/- nitrosourea (65% TMZ group, 68% PCB group	TMZ 150-200 mg/m^2/d for 5 days q28d *or* PCB 125-150 mg/m^2/d for 28 days q56d	5% (TMZ), 5% (PCB)	21% (TMZ), 8% (PCB)	2.8 (TMZ), 1.9 (PCB)	NA	[46]
Phase II, randomized	1st GBM and AA; n=87 (TMZ 5/28), n=81 (TMZ 21/28), n=162 (PCV)	RT	TMZ 200 mg/m^2 for 5 days q28d (TMZ 5/28) *or* TMZ 100 mg/m^2 for 21 days q28d (TMZ 21/28) *or* PCV	NA	NA	5.0[2] (TMZ 5/28), 4.2[2] (TMZ 21/28), 3.6[2] (PCV)	8.5[2] (TMZ 5/28), 6.6[2] (TMZ 21/28), 6.7[2] (PCV)	[69]
Phase II	NA, n=10 (TMZ+BEV), n=13 ETO+BEV)	RT+TMZ/TMZ +BEV+/-other	TMZ 50 mg/m^2/d + BEV 10 mg/kg q2wk *or* ETO 50 mg/m^2/d for 21 days q28d + BEV 10 mg/kg q2wk	0%	4.4%	1.0 (TMZ+BEV), 1.9 ETO+BEV)	NA	[74]
Phase II, randomized	1st, n=39 (TMZ), n=41 (A), n=39 (A+TMZ)	RT+TMZ/TMZ	TMZ 75 mg/m^2/d for 21 days q28d (TMZ) *or* Afatinib 40mg/d (A) *or* Afatinib 40mg/d+ TMZ 75 mg/m^2/d for 21 days q28d (A+TMZ)	19% (TMZ) 2.4% (A), 5% (A+TMZ)	23% (TMZ) 3% (A) 10% (A+TMZ)	1.9 (TMZ) 1 (A) 1.5 (A+TMZ)	10.6 (TMZ) 9.8 (A) 8 (A+TMZ)	[70]
Phase II, randomized	1st, n=105	RT+TMZ/TMZ	TMZ 120 mg/m^2 for 7 days q14d (Arm A) *or* TMZ 80 mg/m^2/d for 21 days q28d (Arm B)	8% (Arm A) 16% (Arm B)	17.1% (Arm A) 25% (Arm B)	NA	9.8 (Arm A) 10.6 (Arm B)	[71]
Single-arm combination therapy trials								
The combination of TMZ+nitrosoureas is reported in Table1								
Phase II	1st, n=15 2nd, n=15 3rd, n=2	RT/TMZ+TMZ+/- other (BEV in n=4)	TMZ 50 mg/m^2/d + BEV 10 mg/kg q2wk	28%	18.8%	3.6	8.5	[72]
Phase I/II	NA, n=15	NA	TMZ 50 mg/m^2/d q3wk + BEV 10 mg/kg q3wk	NA	6.7%	2.4	3.6	[73]
Phase II	1st, n=32	RT+TMZ/TMZ	TMZ 150 mg/m^2 for 7 days q14d+ BEV 10 mg/kg q2wk	40.6%	21.9%	4.2	7.3	[75]
Phase II	NA, n=34 (TMZ+IFN), n=29 (TMZ+pIFN)	RT+/-chemo (no TMZ or IFN)	TMZ 150-200 mg/m^2/d for 5 days q28d + IFN-α2b: 4 MU/ m^2 3x/wk (TMZ+IFN) *and* TMZ 150-200 mg/m^2/d for 5 days q28d + Long-acting PEG-IFN-α2b 0.5 µg/kg/wk (TMZ+pIFN)	12% (TMZ+IFN) 3% (TMZ+pIFN)	31% (TMZ+IFN) 38% (TMZ+pIFN)	3.6 (TMZ+IFN) 4.4 (TMZ+pIFN)	7.2 (TMZ+IFN) 10 (TMZ+ pIFN)	[76]

Phase II	NA, 1-5 treatment lines, n=32	RT+/- chemo (TMZ, BEV and others)	TMZ 50 mg/m²/d + Sorafenib 400 mg 2×/d	3%	9.4%	1.5	9.6	[77]
Phase II	NA, n=34	NA/TMZ (all)	TMZ 472 mg/m^2 q28d +O(6)-BG 1-h infusion of 120 mg/m^2, followed immediately by a 48-h infusion of 30 mg/m^2 q28d	3%	9	1.7	4.5	[78]
Phase I	NA, n=91	RT/chemo	TMZ 200 mg/m^2/d for 5 days q28d + CPT-11 40 mg/m^2 to 375 mg/m^2 IV on weeks 1, 2, 4, and 5 of each 6-wk cycle	12%	27.3%	2.6	NA	[79]
Phase II	1st, n=22	RT+/- chemo (9%, no TMZ)	TMZ 200 mg/m^2 for 5 days q28d + Liposomal DOX 40 mg/m^2 IV on day 1 q4wk	18%	32%	3.6	8.2	[82]
Phase II	NA, n=20	RT+nitrosourea+ CIS	TMZ 200 mg/m^2 on days 2-6 q4wk +CIS 40 mg/m^2, on days 1 and 2 q4wk	10%	35%	4.9	NA	[80]
Phase II	1st, n=50	RT	TMZ 130 mg/m^2 bolus followed by 9 doses of 70 mg/m^2 q12h (total of 5 days) from day 2 q4wk, from 2nd cycle: 100 mg/m^2 mg/m^2 q12h for 5 days q4wk +CIS 75 mg/m^2 on day 1 q4wk	20.4%	34%	4.2	11.2	[81]
Phase I	NA, n=18	NA	ABT-414 0.5-1.5 mg/kg q14d + TMZ 150-200 mg/m^2 for 5 days q28d	22.2%	NA	NA	NA	[83]

Abbreviations: (6)-BG: O6-benzylguanine; A, afatinib; AA, anaplastic astrocytoma; AG, anaplastic glioma; BEV, bevacizumab, CIS, cisplatin; d, day; DOX, doxorubicine; ETO, etoposide; GB, glioblastoma; IFN, interferon; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PCB, procarbacine; PCV, procarbazine, CCNU, and vincristine; PCB: procarbazine, PFS, progression-free survival; pts, patients; q, every; Ref, reference; RT, radiotherapy; TMZ, temozolomide. wk, week;

[1] Data presented for glioblastoma patients only. In case, the study was designed for different patient populations, only the respective data for glioblastoma patients were included in the table

[2] Reporting of data for glioblastoma patients only was not possible due to lack of reporting data seperately in the studies of Berrocal and colleagues [129] with 27 patients with glioblastoma, 15 with anaplastic astrocytoma and 5 with miscellaneous brain tumors and the study of Brada and colleagues [69] with 277 patients with glioblastoma, 53 with anaplastic astrocytoma and 20 with miscellaneous brain tumors.

Table 3. Bevacizumab monotherapy and combination regimens[1/2]

Design	No. of relapse, no. of patients	Pre-treatment	Regimen	ORR (%)	PFS-6 (%)	mPFS (months)	mOS (months)	Ref.
Single-arm monotherapy trials								
Phase II	1st, n=48	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk, addition of CPT-11 at progression	35%	29%	3.7	7.2	[86]
Phase II	1st and other, n=50	RT/TMZ+ TMZ+ other	BEV 15 mg/kg q3wk	NA	25%	2.8	6.5	[87]
Phase II	1st, n=29	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk	27.6%	33.9%	3.3	10.5	[88]
Randomized trials								
Phase II, randomized	1st, n=50 (BEV), n=46 (CCNU), n=44 (BEV+CCNU)	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk *or* CCNU 110 mg/m^2 q6wk *or* BEV q2wk +CCNU 90 (-110) mg/m^2 q6wk	38 (BEV), 5 (CCNU), 34 (BEV+CCNU)	18 (BEV), 11 (CCNU), 41 (BEV+CCNU)	3 (BEV), 2 (CCNU), 11 (BEV+CCNU)	8 (BEV), 8 (CCNU), 11 (BEV+CCNU)	[54]
Phase II, randomized	1st,2nd, 3rd, n=68 evaluable pts	RT/TMZ+ TMZ+/- other	BEV 10 mg/kg q2wk *or* BEV 5 mg/kg q3wk+ CCNU 110 mg/m^2 q6wk	NA	NA	4.1 (BEV), 4.3 (BEV+CCNU)	NA (ITT); Pts with 1st relapse: 8.8 (BEV), 13.1 (BEV+CCNU)	[58]
Phase III, randomized 2:1	1st, n=288 (CCNU+BEV), n=149 (CCNU)	RT/TMZ+TMZ	CCNU 90 mg/m^2 q6wk + BEV 10 mg/kg q2wk *or* CCNU 110 mg/m^2 q6wk	NA	NA	4.2 (CCNU+BEV), 1.5 (CCNU)	9.1 (CCNU+BEV), 8.6 (CCNU)	[56]
Phase II, randomized	1st, n=69 (BEV) 2nd, n=16 (BEV) 1st, n=66 (BEV+CPT) 2nd, n=16 (BEV+CPT)	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk *w/o* CPT-11 340 mg/m2 or 125 mg/m2 q2wk	28 (BEV), 38 (BEV+CPT-11)	42.6 (BEV) 50.3 (BEV+CPT-11)	4.2 (BEV) 5.6 (BEV+CPT-11)	9.2 (BEV) 8.7 (BEV+CPT-11)	[85]
Phase II, randomized	1st, n=55 (BEV), n=55 (BEV+Carbo)	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk *w/o* Carbo (AUC 5) q4wk	6% (BEV), 14% (BEV+Carbo)	18% (BEV), 15% (BEV+Carbo)	3.5 (BEV), 3.5 (BEV+Carbo)	7.5 (BEV), 6.9 (BEV+Carbo)	[84]
Phase II, randomized	1st, n=41 (BEV), n=49 (BEV+VOR)	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk *w/o* VOR 400mg/d for 7 days q2wk	NA	NA	3.6 (BEV), 4.2 (BEV+VOR)	7.0 (BEV), 8.3 (BEV+VOR)	[89]
Phase II, randomized 1:2	NA, n=38 (BEV+P), n=83 (BEV+Dasa)	NA	BEV 10 mg/kg q2wk+P *w/o* Dasa 100 mg twice/d	26.5% (BEV+P), 18.3% (BEV+Dasa)	18.4% (BEV+P), 27.2% (BEV+Dasa)	NA	7.9 (BEV+P), 7.2 (BEV+Dasa)	[90]
Single-arm combination therapy trials								
The combination of BEV+nitrosoureas is reported in Table 1								
The combination of BEV+TMZ is reported in Table 2								
NA	NA, n=11 GB, n=10 other glioma	NA	BEV 5 mg/kg every other wk for 2 doses + CPT-11 125 mg/m^2 qwk for 4 doses, followed by 2-wk rest period	43%	NA	NA	NA	[91]

Design	No. of relapse, no. of patients	Pre-treatment	Regimen	ORR (%)	PFS-6 (%)	mPFS (months)	mOS (months)	Ref.
Phase II	NA, n=23	RT and/or chemo	BEV 10 mg/kg q2wk+ CPT-11 340 mg/m^2 (with EIAED) or 125 mg/m^2 (without EIAED) q2wk	61%	30%	4.6	9.2	[93]
Phase II	NA, n=35	RT/TMZ+ TMZ+ other	*Cohort 1*: BEV 10 mg/kg q2wk + CPT-11 340 mg/m^2 (with EIAED), or 125 mg/m^2 (without EIAED), q2wk (6-wk cycle) *Cohort 2*: BEV 15 mg/kg IV q21d + CPT-11 340 mg/m^2 (with EIAED) or 125 mg/m^2 (without EIAED) on days 1, 8, 22, and 29 (6-wk cycle)	NA	46%[3]	5.5[3]	9.7[3]	[92]
Phase II	NA, n=57	RT/TMZ+TMZ	BEV 10 mg/kg +CPT-11 200 mg/m^2 q2wk	NA	37%	NA	NA	[94]
Phase II	NA, n=32	NA	BEV 10 mg/kg q2wk + CPT-11 340 mg/m^2 IV (with EIAED) 125 mg/m^2 (without EIAED) q2wk	25%	28%	5.2	7.9	[95]
Phase II	1st within last 6 months of first-line treatment, n=43 (n=32 evaluable)	RT/TMZ+ TMZ	BEV 5-10 mg/kg q2wk + CPT-11 340 mg/m^2 IV (with EIAED) 125 mg/m^2 (without EIAED) q2wk + CET 400 mg/m^2 IV as loading dose, followed by 250 mg/m^2/wk	34%	30%	3.7	6.7	[96]
Phase II	1st, n=27, 2nd, n=11, 3rd, n=2	RT/TMZ+ TMZ+ other (no BEV)	BEV 10 mg/kg q2wk + CPT-11 340 mg/m^2 IV (with EIAED) 125 mg/m^2 (without EIAED) q2wk + Carbo (AUC 5) q4wk	33%	46.5%	5.9	8.3	[97]
Phase II	1st, n=14, 2nd, n=8 3rd, n=5	RT+chemo	BEV 10 mg/kg q2w + ETO 50 mg/m^2 daily for 21 consecutive days each month	22%	44.4%	4.1	10.2	[98]
Phase II	1st: 52%; 2nd: 36%; 3rd: 12%	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk + ERL 500 mg/kg/d (with EIAED) or, 200 mg/kg/d (without EIAED)	50%	29.2%	4.1	10.3	[100]
Phase II	NA, n=13	RT/TMZ+ TMZ+BEV	BEV 10 mg/kg q2wk starting on day 8 + temsirolimus 25 mg qwk starting on day 1	0%	NA	1.8	3.5	[99]
Phase II	NA, n=54	RT/TMZ+ TMZ+/- other	BEV 5 mg/kg q2wk + Sorafenib 100-200 mg/d	18.5%	20.4%	2.9	5.6	[101]
Phase II	≤2 relapses, n=24 (interim analysis)	NA (No anti-VEGF, no HDAC-I)	BEV 10 mg/kg q2wk +Panobinostat 30mg 3 times/wk	29.2%	30.4%	5	9	[102]
Phase II	NA, n=40	NA	BEV 10 mg/kg q2wk +VOR 400mg/d for 7 days q2wk	22.5%	30%	NA	10.4	[103]

Abbreviations: AUC, area under the curve; BEV, bevacizumab; CET, cetuximab; Carbo, carboplatin; CPT-11, irinotecan; d, day; Dasa: Dasatinib; EIAED, enzyme-inducing antiepileptic drugs; ERL, erlotinib; ETO, etoposide; GB, glioblastoma; HDAC-I: histone deacetylase-inhibitors, ITT: intention-to-treat-population; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; P: placebo; PFS, progression-free survival; pts, patients; q, every; Ref, reference; RT, radiotherapy; TMZ, temozolomide,; VEGF: vascular endothelial growth factor, VOR: vorinostat; w/o, with or without; wk, week;

[1] Data presented for glioblastoma patients only. In case, the study was designed for different patient populations, only the respective data for glioblastoma patients were included in the table

[2] Reporting of data for glioblastoma patients only was not possible due to lack of reporting data for separately for one study [91] where combined data of patients were presented (11 patients with glioblastoma and 10 patients with anaplastic glioma)

[3] Data presented for both cohorts combined

Table 4: Targeted agents, monotherapy and combination regimens[1/2]

Design	No. of relapse, no. of patients	Pre-treatment	Regimen	Target	ORR	PFS-6	mPFS (months)	mOS (months)	Ref.
Phase II	NA, n=20	RT+chemo	Gefitinib 250 qd and everolimus 70 mg qw	EGFR (Gefitinib), mTOR (Everolimus)	14%	NA	2.6	5.8	[108]
Phase II	NA, n=31	RT or RT/TMZ+ TMZ	Cediranib 45 mg/d	VEGFR1-3, c-Kit, PDGFR	27%	25.8	3.8	7.5	[106]
Phase II	NA/34% 2nd, total: n=78 (125mg), n=46 (175mg)	NA/Previous AAT (n=42)	XL184 125 mg *or* 175 mg qd	c-MET, VEGFR2, RET	NA	NA (125 mg) 21% (175 mg)	NA	NA	[134, 135]
Phase II	NA, n=35	NA	Pazopanib 800 mg qd	VEGFR1-3, c-Kit, PDGFR	6%	3%	2.8	NA	[136]
Phase II	1st, n=37	RT+chemo	Sagopilone16 mg/m^2 q21d	Microtubule	0%	6.7%	1.4	7.6	[137]
Phase II	1st, n=39 2nd, n=3 (excluded from efficacy analysis)	RT/TMZ+ TMZ	Aflibercept 4 mg/kg q2wk	VEGF, PlGF	18%	7.7	2.8	9.0	[138]
Phase II	NA, n=66	NA	VOR 400mg/d for 14 days of a 21-day cycle	Histone deacetylase	3%	15.2%	1.9	5.7	[113]
Phase II	≤3 relapse, n=16	RT/TMZ+ TMZ+/-other (BEV 48%)	AMG-102: 10 or 20mg/kg q2k	HGF	2%	NA	1.0 (10 mg) 1.2 (20 mg)	6.5 (10 mg) 5.4 (20 mg)	[139]
Phase II	1st (n=18), 2nd (n=7), 3rd or more (n=7)	RT+chemo+/ -others	Vandetanib 300 mg qd	VEGFR2, EGFR, "rearranged-during-transfection oncogene"	13%	6.5%	1.3	6.3	[140]
Phase II	≤2 relapse, n=16	RT/TMZ+ TMZ+/-other	Sunitinib 50mg/d for 4 wk every 6 wks	VEGFR1-2, c-Kit, PDGFR, FLT3,CSF-1R, RET	0%	16.7%	1.4	12.6	[141]
Phase II	NA, n=37	NA	VOR 400mg/d for 14 days of a 21-day cycle Bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11	Histone deacetylase (VOR), Proteasom (Bortezomib)	3%	0%	1.5	3.2	[114]
Phase II	NA, n=56	RT+chemo	Erlotinib 150 mg/d, sorafenib 400mg twice/d	EGFR (Erlotinib), VEGFR, PDGFR, Raf kinases	5%	14%	2.5	5.7	[115]
Phase I	NA, n=18	NA	ABT-414 0.5-1.5 mg/kg q14d + TMZ 150-200 mg/m^2 for 5 days q28d	EGFR (ABT-414)	22.2%	NA	NA	NA	[83]
Phase II	1st, n=13 2nd, n=12	RT/TMZ+ TMZ (n=13), BEV at 1st relapse (n=12)	Nintedanib 200 mg bid	VEGFR1-3, FGFR1-3, PDGFR	0%	NA	1	6	[142]
Phase II	NA, n=41	RT+ chemo, others	Pazopanib 400 mg qd, Lapatinib 1000 mg ad	VEGFR1-3, c-Kit, PDGFR (Pazopanib), EGFR (Lapatinib)	5%	7.5%	1.9	NA	[143]
Phase II	NA, n=32 BEV naïve, n=31 BEV resistant	RT/TMZ+ TMZ +/- BEV or other	Sunitinib 37.5 mg qd	VEGFR1-2, c-Kit, PDGFR, FLT3, CSF-1R, RET	10% (BEV-naïve) 0% (BEV-resistant)	10.4% (BEV-naïve) 0% (BEV-resistant)	1 (BEV-naïve) 1 (BEV-resistant)	9.4 (BEV-naïve), 4.4 (BEV-resistant)	[144]
Phase II	≤2 relapse, n=31 (BEV-naïve), n=25 (previous BEV)	RT/TMZ+ TMZ+/-other	Verubulin 3.3 mg//m^2 qwk for 3 wks, every 4 wks	Microtubule destabilizing, vascular disruption	10%(BEV-naïve), 4.2% (previous BEV)	14%(BEV-naïve), 8% (previous BEV)	1.6 (BEV-naïve), 0.8 (previous BEV)	9.4 (BEV-naïve), 3.4 (previous BEV)	[145]

Phase II	1st, n=50, overexpression of at least 2 putative dasatinib targets	RT/TMZ+ TMZ	Dasatinib 100 mg -200 twice/d,	SRC, c-KIT, EPHA2, PDGFR	0%	6%	1.7	7.9	[111]
Phase II	NA, n=7 (Arm A), n=15 (Arm B, 12 evaluable)	RT/TMZ+ TMZ	3 doses of Selinexor 50 mg/m^2 prior to surgery, Selinexor 50 mg/m^2 after surgery (Arm A) *and* Selinexor 50 mg/m^2 q2wk (Arm B)	Nuclear retention via XPO1 of p53, pRB, CDKN2A, p21 and FOXO	17%	NA	NA	NA	[109]
Phase II	1st, n=33	RT/TMZ+ TMZ	PX-866 8mg/d	PI3K	3%	17%	NA	NA	[110]
Randomized trials									
Phase II, randomized	1st , n=41 (500mg) n=40 (200mg)	RT, TMZ and others	CIL 500 *or* 2000 mg, 2×/wk	αvβ3/αvβ5 integrins	5% (500 mg) 13% (2000 mg)	10% (500 mg)^2 15% (2000 mg)^2	NA	6.5^2 (500 mg) 9.9^2 (2000 mg)	[112]
Phase II, randomized	1st, CTR: n=29 (BCNU), n=27 (TMZ), n=52 evaluable; n=54 (ERL)	RT+/-Chemo (64% CTR/ 65% ERL)	CTR (BCNU 60 mg/m^2 on days 1-3 q8wk (max 5 cycles) *or* TMZ 150-200 mg/m^2 (5/28) *or* ERL 150-200 mg/d	EGFR (ERL)	10% (CTR), 4% (ERL)	24% (CTR), 11% (ERL)	2.4 (CTR), 1.8 (ERL)	7.3 (CTR), 7.7 (ERL)	[57]
Phase II, randomized	1st and 2nd , total n=26	RT+ chemo	CIL 500 *or* 2000 mg × 3 doses, resection, then 2000 mg 2×/wk	αvβ3/αvβ5 integrins	NA	12% (both arms)	1.9 (both arms)	NA	[146]
Phase III, double-blind, randomized 1:2:2	1st, n=65 (CCNU) n=131 (CED), n=129 (CED+CCNU)	RT/TMZ+ TMZ	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	VEGFR1-3 and PDGFR (CED)	8% (CCNU), 14 %(CED), 16%, (CED+ CCNU)	24.5% (CCNU), 16% (CED), 34.5 % (CED+ CCNU)	2.7 (C2CNU), 3.1 (CED11), 4.2 (CED+ CCNU)	9.8 (CCNU), 8.0 (CED), 9.4 (CED+ CCNU)	[52]
Phase III, randomized 2:1	1st: n=70 (CCNU), n=129 (Enzastaurin) 2nd: n=21 (CCNU), n=45 (Enzastaurin)	RT+/-Chemo (NA, no nitrosourea)	CCNU 100-130 mg/m^2 q6wk *or* Enza 500 mg/d (1125 mg on day 1)	Protein kinase C, PI3K, AKT	4% (CCNU), 3% (Enza)	19% (CCNU), 11% (Enza)	1.6 (CCNU), 1.5 (Enza)	7.1 (CCNU), 6.6 (Enza)	[53]
Phase II, randomized 2:1:1, placebo-controlled	NA, n=79 (CCNU+G), n=39 (G), n=40 (CCNU+P)	NA	CCNU q6w + Galunisertib (CCNU+G) *or* Galunisertib (300mg/d) for 14 days q28d alone (G) *or* CCNU q6w +P (P+CCNU)	TGFβR1 (G)	1% (CCNU+G), 5% (G), 0% (CCNU+P)	NA	1.8 (CCNU+G), 1.8 (G), 1.9 (CCNU+P)	6.7 (CCNU+G), 8 (G), 7.5 (CCNU+P)	[55]
Phase II, randomized	1st, n=39 (TMZ), n=41 (A), n=39 (A+TMZ)	RT/TMZ+ TMZ	TMZ 75 mg/m^2/d for 21 days q28d (TMZ) *or* Afatinib 40mg/d (A) *or* Afatinib 40mg/d+ TMZ 75	ErbB, EGFR (A)	19% (TMZ) 2.4% (A), 5% (A+TMZ)	23% (TMZ) 3% (A) 10% (A+TMZ)	1.9 (TMZ) 1 (A) 1.5 (A+TMZ)	10.6 (TMZ) 9.8 (A) 8 (A+TMZ)	[70]

			mg/m^2/d for 21 days q28d (A+TMZ)						
Phase II, randomized	1st, n=41 (BEV), n=49 (BEV+VOR)	RT/TMZ+ TMZ	BEV 10 mg/kg q2wk *w/o* VOR 400mg/d for 7 days q2wk	Histone deacetylase	NA	NA	3.6 (BEV), 4.2 (BEV+VOR)	7.0 (BEV), 8.3 (BEV+VOR)	[89]
Phase II, randomized 1:2	NA, n=38 (BEV+P), n=83 (BEV+Dasa)	NA	BEV 10 mg/kg q2wk+P *w/o* Dasa 100 mg twice/d	SRC, c-KIT, EPHA2, PDGFR (Dasa)	26.5% (BEV+P), 18.3% (BEV+Dasa)	18.4% (BEV+P), 27.2% (BEV+Dasa)	NA	7.9 (BEV+P), 7.2 (BEV+Dasa)	[90]

Abbreviations: A, Afatinib; AAT, antiangiogenic therapy, BEV, bevacizumab; CCNU, lomustine; CED, cediranib; CIL, cilengitide; CSF-1R, Colony stimulating factor 1 receptor, d, day; Dasa: Dasatinib; EGFR, epidermal growth factor receptor; EPHA2, ephrin type-A receptor 2; ErbB, erythroblastic leukemia viral oncogene;, ERL, erlotinib; FGFR, fibroblast growth factor receptor; G: galunisertib; HGF, hepatocyte growth factor/scatter factor; c-MET, hepatocyte growth factor receptor; mOS, median overall survival; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin, NA, not available; P, placebo; PDGF-R, platelet-derived growth factor receptor; PFS, progression-free survival; PI3K, phosphatidylinositide 3-kinase, PlGF, placental growth factor; pts, patients; q, every; Ref, reference; TMZ, temozolomide; TGFβR1, transforming growth factor-β-receptor-1; VEGF, vascular endothelial growth factor VEGFR, receptor to vascular endothelial growth factor; VOR, vorinostat; FLT-3, fms-like tyrosine kinase 3; w/o, with or without; wk, week;

[1] Data presented for glioblastoma patients only. In case, the study was designed for different patient populations, only the respective data for glioblastoma patients were included in the table

[2] Reporting of data for glioblastoma patients only was not possible due to lack of reporting data seperately for one study where central histopathology review showed that 6 patients had either anaplastic astrocytoma or low-grade glioma [112]

7. Vitae

Katharina Seystahl, MD works as a Physician-Scientist at the Department of Neurology at the University Hospital Zurich. Research interests include clinical and molecular neuro-oncology with focus on antiangiogenic therapies and involvement of TGF-β in the pathogenesis of glioblastoma.

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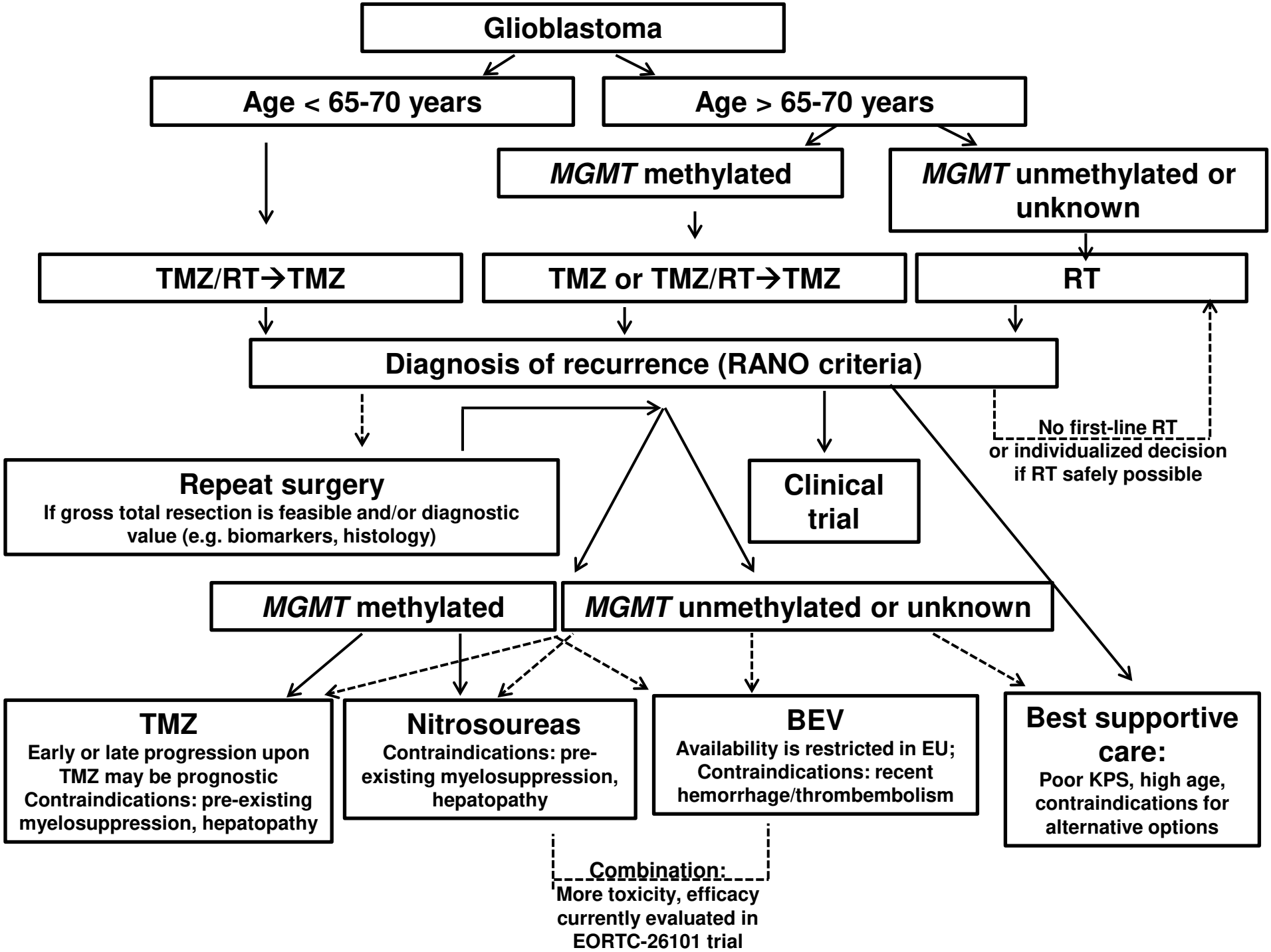
Figure 1: Approach for individualized treatment decisions in patients with glioblastoma.

Continuous arrows indicate evidence-based current clinical practice. Dashed arrows represent possibilities of individual decision-making which has still to be confirmed. Abbreviations: CCNU, lomustine; KPS, Karnofsky performance scale; RT, radiotherapy; TMZ, temozolomide; TMZ/RT→TMZ, radiotherapy with concomitant and maintenance TMZ


Glioblastoma
Age < 65-70 years
Age > 65-70 years
MGMT methylated
MGMT unmethylated or unknown
TMZ/RT→TMZ
TMZ or TMZ/RT→TMZ
RT
Diagnosis of recurrence (RANO criteria)
No first-line RT or individualized decision if RT safely possible
Repeat surgery
If gross total resection is feasible and/or diagnostic value (e.g. biomarkers, histology)
Clinical trial
MGMT methylated
MGMT unmethylated or unknown
TMZ
Early or late progression upon TMZ may be prognostic
Contraindications: pre-existing myelosuppression, hepatopathy
Nitrosoureas
Contraindications: pre-existing myelosuppression, hepatopathy
BEV
Availability is restricted in EU;
Contraindications: recent hemorrhage/thrombembolism
Best supportive care:
Poor KPS, high age, contraindications for alternative options
Combination:
More toxicity, efficacy currently evaluated in EORTC-26101 trial